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EDITORIAL COMMENT

Quantifying Atherosclerosis by "3D" Ultrasound Works!

But There Is Work to Be Done*

Tasneem Z. Naqvi, MD

Imaging-based assessment of atherosclerosis to predict incident cardiovascular disease (CVD) instead of a risk factor–based approach has been proposed as a way to implement preventive intervention and thwart the increasing CVD toll (1). Intima-media thickness (IMT) of exposed large vessels, such as the carotid arteries, predicts future CVD better than risk factors alone (2). However, wide variability in ability of IMT to predict future CVD events was found amongst studies, leading to uncertainty regarding its utility (3), which is reflected in consensus statements and guidelines. The 2010 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (4) gave carotid IMT assessment a Class IIa (benefit greater than risk) indication in subjects with intermediate-risk Framingham Risk Scores (FRS), whereas the 2013 guidelines gave it a Class III indication (should not be done) (5).

Subsequent studies showed that focal atherosclerosis defined by plaques conferred a higher CVD risk than IMT (6–8). The published reports (3,4,9,10) show that if an ultrasound (US) IMT imaging protocol is less comprehensive or excludes assessment of plaque, its predictive power is weakened. More recent studies IMT has been shown to have a much weaker predictive power for CVD events than coronary artery calcification (CAC) (11,12). However, 2-dimensional (2D) IMT and binary assessment of plaque only captures an incomplete image of atherosclerosis, as compared to the 3-dimensional (3D) assessment of coronary plaque calcification by coronary computed tomography.

2D carotid plaque area performed far better than IMT assessment in the prediction of ischemic stroke in a large cohort of adults (13). Assessment of 3D plaque area by US would be better than 2D plaque area method to quantify atherosclerosis, however, no study has demonstrated whether assessment of plaque burden by 3D US is feasible and accurate enough compared with a direct 3D assessment of coronary plaque by CAC for prediction of CVD events.

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The BioImage Study by Baber et al. (14) in this issue of the *Journal* is a landmark large, prospective study of asymptomatic men and women (N = 7,687, age 69 ± 6 years) that assessed total carotid artery plaque burden using both a modified "3D" US assessment of bilateral carotid arteries CAC. The purpose was to predict near-term (3-year) atherothrombotic events by comparing imaging biomarkers from 2 different vascular beds. The results showed that 3D carotid plaque burden was comparable to CAC plaque burden in predicting death and myocardial infarction, as well as angina and coronary revascularization, over a mean 2.7-year follow-up. If confirmed, these results may have broad implications, because US is readily available, portable, without risk, readily repeatable, and does not expose patients to radiation.

Importantly, in the current study, 60% of the overall study cohort and one-half of the low-FRS subjects had an atherosclerotic burden by either imaging test—a sobering statistic. Both CAC and 3D carotid US reclassified individuals far better than the risk factor–based approach and had a similar clinical net reclassification index. More than 40% of subjects with intermediate FRS and up to 12% of subjects with any FRS were classified appropriately as higher

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From the Echocardiography Laboratory and Division of Cardiology, Mayo Clinic, Scottsdale, Arizona. Dr. Naqvi has received research grants from Esaote North America Inc., Cardionexus Corporation, Panasonic Healthcare, and Philips Healthcare.

or lower risk by imaging-based assessment of atherosclerosis. Reassuringly, both tests reclassified over one-half of the patients in whom events did not occur as low risk across all FRS categories (3,152 by CAC and 2,792 by plaque of 5,726 subjects). In the low-risk and intermediate-risk cohorts, defined by FRS or by the new pooled cohort equation, without events, US overclassified patients as higher-risk compared with CAC. However, among the 82 subjects in whom primary events occurred and 216 subjects in whom secondary events occurred, each test classified a third of subjects as low risk. An important finding is the incremental impact of systemic atherosclerosis on short-term risk. Thus, the presence of atherosclerosis in 2 vascular beds conferred a higher risk than in 1 bed alone, and across all risk categories, the gradient of risk between increasing CAC or plaque remained independent of one another and of risk factors.

There are limitations to the study by Baber et al. (14). The primary endpoint occurred in only 82 (1.5%) of the study cohort and secondary endpoint in 216 (4.2%). This low event rate is related to a short follow-up (mean 2.7 years) and probable risk modification as a result of statin use during enrollment, which was not detailed in the study. The plaque assessment was not real-time 3D using a 3D transducer, but a combination of 2D images obtained from a 2D transducer (with attendant increased post-processing times), because true 3D methods were not fully developed at the start of the study. In addition, plaque was only assessed in the short-axis views, which may miss or poorly quantify plaque in tortuous or deep vessels, and may not delineate medial and lateral wall plaques because of the poor lateral resolution of US. Recent data show that direct 3D assessment and quantification of carotid plaque is feasible and can be used clinically (15). An unanswered question is whether the imaging-based results would change in younger subjects who have not yet developed plaque calcification, but have noncalcified plaque that is detectable by US. The threshold of significance for plaque burden and the effect of aging on this threshold also remain unclear, and should be addressed by further studies. In addition, any conclusions drawn from the study by Baber et al. (14) apply in the short term, only to short-term adverse events of atherothrombosis and may be different if the subjects were followed longer term. In particular the predictive ability of both tests may diverge with longer follow up, considering that a higher percent of subjects with lower and intermediate FRS were classified by ultrasound as higher risk compared to CAC.

How should these new imaging modalities be used? On the basis of data from this study, direct imaging assessment of atherosclerosis in at least 1 vascular bed is far superior to a risk factor-based approach in allocating middle-aged to older individuals to the correct CVD risk category. Because of the lack of radiation, US imaging may be more suitable for longitudinal life-long surveillance if no plaque burden is identified in either vascular bed at baseline and may be a first-line test in younger individuals and in women in whom plaque calcification may not have developed, although the current study in an older cohort of subjects does not address this question.

The new Framingham Cohort Equations would recommend nearly 50% of U.S. adults for statin therapy (16). Would this be safer, more cost effective, and reduce CVD death rates compared with an imaging-based approach that correctly reclassified more than 40% of subjects with intermediate FRS? The future of 3D US is bright, with expected near-term improvements in frame rate and online data processing availability. This would provide a faster, more accurate, and repeatable test to detect and quantify atherosclerosis in its earliest stages, as well as monitor treatment effects on atherosclerosis in individual patients. Longer-term follow-up data from the current study and future studies using real-time 3D US would be of great interest. In the meantime, the study by Baber et al. (14) brings an imaging-based approach for detecting individuals at higher risk of future CVD closer to clinical application.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Tasneem Z. Naqvi, Division of Cardiology, Department of Medicine, Mayo Clinc, 13400 East Shea Boulevard, Scottsdale, Arizona 85259. E-mail: naqvi.tasneem@mayo.edu.

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